2-(*s*-HYDRINDACEN-4-YL)ETHYLAMINES AND THEIR 1-METHYL AND 1,1-DIMETHYL DERIVATIVES; SYNTHESIS AND PHARMACOLOGICAL SCREENING*

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4-Chloromethyl-*s*-hydrindacene (*I*) was transformed *via* the nitrile *II* to (*s*-hydrindacen-4-yl)acetic acid (*VII*) which was further converted to derivatives *VIII*—*XI*. Alkylation of diethyl formamidomalonate with the chloride *I* gave the ester *III* which was transformed in two steps to (*s*-hydrindacen-4-yl)alanine (*V*). Reduction of the nitrile *II* gave 2-(*s*-hydrindacen-4-yl)ethylamine (*XIV*) which yielded by methylation the N,N-dimethyl derivative *XV*. The amines *XVI* and *XVII* were obtained by reduction of the piperazides *X* and *XI*. Acylation of diethyl malonate with the acid chloride *VIII*, the following hydrolysis and decarboxylation resulted in (*s*-hydrindacen-4-yl)-acetone (*XII*). Its oxime *VI* was the basis for synthesis of 1-(*s*-hydrindacen-4-yl)-2-propylamines *XX*, *XXII* and *XXIII*. Treatment of the ketone *XII* with methylmagnesium iodide led to the alcohol *XXIV* giving by the Ritter reaction the formamide derivative *XXV* which was the key intermediate in the preparation of 1-(*s*-hydrindacen-4-yl)-2-methyl-2-propylamines *XXVI*—*XXVIII*. The central activity of the amines prepared is rather weak. The amphetamine derivatives *XX* and *XXIII* have anorectic and antireserpine effects. For some of the products (*XIV*—*XVII*, *XXVII*), adrenolytic and brief hypotensive activity was shown. In some cases (*XV*, *XX*, *XXII*, *XXVII*), local anaesthetic and spasmolytic effects were detected which are not structure-specific.

After synthesis and pharmacological screening of amines of the *s*-hydrindacene series in which the amino group was connected to the aromatic nucleus of the *s*-hydrindacene system (position 4) either directly[1] or through a single carbon atom[2], we arrived now at a systematic investigation of compounds in which the amino group is separated from the skeleton by a two-membered carbon chain. The compounds described in our previous paper[3] had an oxygen function on the carbon adjacent to the nucleus. In the present communication, substances are described having in the mentioned position a methylene group; we are thus dealing here with the *s*-hydrindacene analogues of phenethylamine, amphetamine, phentermine and their N-substituted derivatives.

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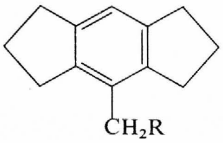
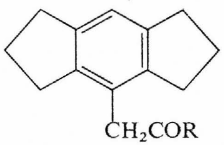
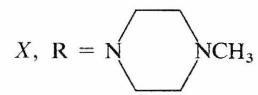
The common starting compound in the synthesis of these substances was 4-chloromethyl-*s*-hydrindacene (*I*), the synthesis of which was described in a previous communication[2]. Its reaction with sodium cyanide in dimethyl sulfoxide (for the method, *cf.*[4,5]) gave the nitrile *II* which was first hydrolyzed with acid to (*s*-hydrindacen-4-yl)-acetic acid (*VII*). This acid yielded by treatment with thionyl chloride the acid chloride *VIII*, the ethanolysis of which in the presence of pyridine led to the ethyl ester *IX*. Its reduction with lithium aluminium hydride in ether resulted in the alcohol *XIII*. Reactions of the chloride *VIII* with 1-methylpiperazine and 1-(2-hydroxyethyl)piperazine gave the piperazides *X* and *XI*. By reduction of the nitrile *II* with lithium aluminium hydride, the phenethylamine analogue *XIV* was obtained in an almost theoretical yield, giving by methylation with formaldehyde and formic acid the N,N-dimethyl derivative *XV*. Reduction of the piperazides *X* and *XI* with lithium aluminium hydride resulted in piperazine derivatives *XVI* and *XVII*.

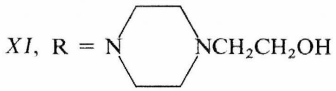


I, R = Cl
II, R = CN
III, R = $C(COOC_2H_5)_2$ | NHCHO
IV, R = $C(COOH)_2$ | NHCHO
V, R = $CH(NH_2)COOH$
VI, R = $C(=NOH)CH_3$



VII, R = OH
VIII, R = Cl
IX, R = OC_2H_5

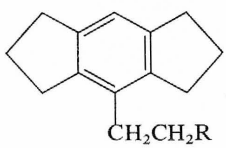




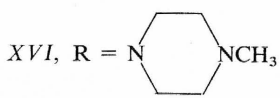
XII, R = CH_3

The acid chloride *VIII* reacted with the ethoxymagnesium derivative of diethyl malonate and the product was processed by acid hydrolysis with simultaneous double decarboxylation (for method, *cf.*[6,7]) giving (*s*-hydrindacen-4-yl)acetone (*XII*). Chromatography of the distillation residue after the ketone *XII* separated two other substances. The less polar one, having a lower melting point, corresponded according to analysis to the composition $C_{16}H_{20}O_3$. The ^{1}H-NMR spectrum was in agreement and showed the presence of 20 protons: 12 H of the alicyclic part of the hydrindacene skeleton, 2 H of a further $ArCH_2$ group and 6 H corresponding to two different methyl groups. There was first no explanation for the absence of the aromatic proton and for the localization of one of the methyl groups. A surprising solution

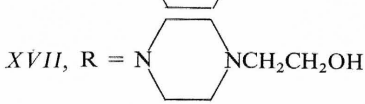
was brought by the mass spectrum with the molecular ion *m/e* 260 corresponding to the empirical formula $C_{16}H_{20}OS$. The supplementary sulfur determination confirmed its presence. The mentioned facts led to a proposal of the structure *XVIII* which is in agreement with analysis and all of the spectra recorded. There was only the question how the methylthio group could enter the product. In this line, we came to the conclusion that the origin of the methylthio group on the nucleus was already the reaction of chloride *I* with sodium cyanide in dimethyl sulfoxide. As a by-product, (8-methylthio-*s*-hydrindacen-4-yl)acetonitrile was evidently formed, which underwent as an impurity of the crude nitrile *II* further reactions with this compound. In the literature, we mentioned two papers describing the reaction of dimethyl sulfoxide with an activated position of the aromatic nucleus in the presence of acid (hydrochloric acid or hydrogen chloride). In the first one[8], phenol was the aromatic acceptor and the substitution proceeded into the *para*-position; in the second[9], 2-phenylindoles were involved and the sulfur substituent entered position 3. In both cases, the dimethylsulfonium salts are the primary products which are additionally thermically cleaved. In our case, the only acid present was hydrogen cyanide formed by hydrolysis of sodium cyanide.



XIII, R = OH
XIV, R = NH_2
XV, R = $N(CH_3)_2$



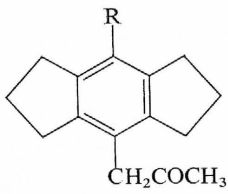
XVI, R =



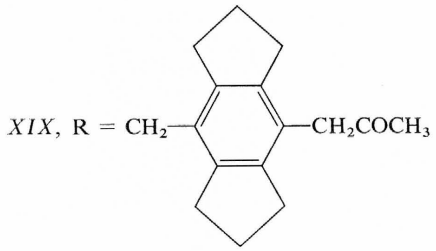
XVII, R =

The solution of structure of the second substance from the distillation residue after the ketone *XII*, having a higher melting point than the foregoing compound and being more polar, gave also a surprising results. Analysis of this substance, in agreement with its mass spectrum, established its empirical formula as $C_{31}H_{36}O_2$ and the ^{1}H-NMR spectrum agrees with its formulation as the bis(*s*-hydrindacen-4-yl)-methane derivative *XIX*. In this case, we suppose that the origin of this substance should be already in an impurity of the starting 4-chloromethyl-*s*-hydrindacene (*I*) (ref.[2]). It is necessary to note that the reaction mixture formed by chloromethylation of *s*-hydrindacene was subjected to careful chromatographic analysis but among

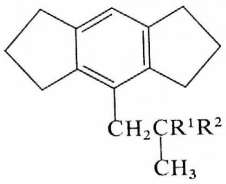
the six isolated and identified products, bis(8-chloromethyl-*s*-hydrindacen-4-yl)methane, necessary for the formation of compound *XIX*, was not found[2].



XVIII, R = SCH_3



The ketone *XII* was transformed to the oxime *VI* which was reduced with sodium and ethanol to the amphetamine analogue *XX*. The formamido derivative *XXI*, obtained by formylation with ethyl formate in an autoclave at 120–130°C, was reduced with lithium aluminium hydride to the methylamino compound *XXII*. The dimethylamino analogue *XXIII* resulted from a methylation of the primary amine *XX* with formaldehyde and formic acid. Treatment of the ketone *XII* with methylmagnesium iodide gave the tertiary alcohol *XXIV* from which the formamido derivative *XXV* was obtained by Ritter reaction with sodium cyanide in a mixture



XX, R^1 = H, R^2 = NH_2
XXI, R^1 = H, R^2 = NHCHO
XXII, R^1 = H, R^2 = $NHCH_3$
XXIII, R^1 = H, R^2 = $N(CH_3)_2$
XXIV, R^1 = CH_3, R^2 = OH

XXV, R^1 = CH_3, R^2 = NHCHO
XXVI, R^1 = CH_3, R^2 = NH_2
XXVII, R^1 = CH_3, R^2 = $NHCH_3$
XXVIII, R^1 = CH_3, R^2 = $N(CH_3)_2$
XXIX, R^1 = CH_3, R^2 = $^{(+)}N(CH_3)_3$ $I^{(-)}$

of acetic and sulfuric acid (analogy[10]). Its alkaline hydrolysis led to the phentermine analogue *XXVI*, whereas the reduction with lithium aluminium hydride resulted again in the corresponding secondary amine *XXVII*. Methylation of a mixture of the primary amine *XXVI* and the secondary amine *XXVII*, carried out similarly as in the case of synthesis of compound *XXIII*, gave the dimethylamino derivative *XXVIII*,

transformed in the usual way to the methiodide *XXIX*. Alkylation of diethyl formamidomalonate[11,12] with 4-chloromethyl-*s*-hydrindacene[2] gave the ester *III*, the alkaline hydrolysis of which resulted in the formamidomalonic acid *IV*. The following acid hydrolysis proceeded with simultaneous decarboxylation, the product being (*s*-hydrindacen-4-yl)alanine (*V*).

TABLE I

Pharmacological Screening of *s*-Hydrindacene Derivatives (doses in mg/kg)

Compound	Code number	Administration	Acute toxicity LD_{50}[a]	Basic dose D[b]	CNS effects	Further effects
VII	VÚFB-10.708	oral	590[c]	50	—	*d*
XIV-HCl	VÚFB-10.709	oral	600	120	*e*	*f*,*g*
XV-HCl	VÚFB-10.710	*i.v.*	30	6	*h*	*i*,*j*,*k*
XVI-2 HCl[l]	VÚFB-12.241	*i.v.*	75	15	*m*	*i*
XVII-2 HCl[l]	VÚFB-12.243	*i.v.*	75	15	*n*	*i*
XX-HCl	VÚFB-12.265	*i.v.*	35	7	*o*	*k*,*p*
XXII-HCl	VÚFB-12.266	*i.v.*	25	5	*q*	*j*,*k*,*r*
XXVI-HCl	VÚFB-12.267	oral	1 000	200	*s*	—
XXVII-HCl	VÚFB-12.268	*i.v.*	40	8	*t*	*r*,*u*
XXVIII-HCl	VÚFB-12.304	oral	750	150	—	—

[a] Orientation acute toxicity was determined in mice, in groups by 5 animals; the perishing was followed for the intravenously administered compounds for 3 days and for the orally administered ones for 5 days. [b] Dose in which the compound was administered in the *in vivo* tests. [c] In this case, the toxicity was estimated in groups by 10 animals and the perishing followed for a period of 7 days. [d] The compound was tested in rats on two models of inflammation; in the dose D it had only a weak effect in the test of kaolin oedema (inhibition of the oedema by 9%) and was inactive in the test of adjuvant oedema; the same dose of phenylbutazone inhibits the same models of inflammation by 24, and 28%, respectively. [e] Doses higher than D bring about ataxia and tremor in mice; in doses of 50—120 mg/kg, the substance had anticonvulsant activity in mice towards pentatrazole (comparable with the effect of phenytoin). [f] In doses of 10—50 mg/kg, it decreases the blood pressure of normotensive rats by 10%. [g] In doses of 50—120 mg/kg, it decreases the blood sugar level in rats by 20%. [h] In the dose D, administered subcutaneously to mice, it showed stimulant activity (increased the motility). [i] In normotensive rats, the dose D brings about deep and brief drop of blood pressure, as well as inhibition of the adrenaline hypertensive reaction. [j] In concentrations of 5—50 μg/ml, it decreases heart inotropy and frequency by 25% (isolated rabbit atrium). [k] In a concentration of 0·1—0·5% in the test of infiltration anaesthesia in rabbits, it brings about a complete anaesthesia in 50% of the animals (2—10 times more active than procaine). [l] Hemihydrate. [m] In doses higher than D, it brings about in mice first excitation, followed by depression. [n] Like *e* but inactive as an anticonvulsant. [o] In doses higher than D signs of central depression; in the dose D, administered intraperitoneally, it shows antireserpine

activity in mice towards reserpine ptosis, as well as against hypothermia (about 10% of the amphetamine activity); has anorectic activity in mice: in an oral dose of 35 mg/kg, it decreases the intake of food by 50% (in comparison with the control) without increasing the motility. [p] In a concentration of 10 μg/ml, it diminishes barium chloride contractions of the isolated rat duodenum by 50% (approaches the effect of papaverine). [q] In doses higher than D, it brings about in mice central depression, ataxia and convulsions. [r] On the isolated rat duodenum, it inhibits in concentrations 1—10 μg/ml acetylcholine and barium chloride contractions by 50% (1% of atropine activity, 100% of papaverine activity). [s] In a dose lower than D, it has antireserpine effect in mice towards reserpine ptosis, as well as towards hypothermia; in a dose of 50 mg/kg, it has a significant anorectic effect in mice — it decreases the food intake by 50% (in comparison with the control) and simultaneously has only a very mild motility potentiating effect. [t] In doses higher than D had a mild central depressant activity in mice (inhibits motility in known surroundings). [u] In a dose of D/2, it decreases in normotensive rats the adrenaline hypertensive response by 50% (adrenolytic action); in a concentration of 5 μg/ml, it decreases heart frequency by 25% (isolated rabbit atrium).

TABLE II

Antimicrobial Activity of *s*-Hydrindacene Derivatives *in vitro* (minimum inhibitory concentrations in μg/ml are shown)

Compound[a]	Microorganism[b]										
	1	2	3	4	5	6	7	8	9	10	11
VII	>100	>100	>100	>100	>100	>100	100	100	50	100	100
X[c]	>100	>100	>100	>100	>100	>100	100	100	100	100	>100
XI[d]	>100	>100	>100	>100	>100	>100	>100	100	50	100	100
XIV	100	>100	>100	>100	100	>100	25	100	100	100	>100
XV	>100	>100	>100	>100	>100	>100	50	100	50	100	>100
XVI	50	50	100	>100	>100	>100	100	100	50	100	100
XVII	50	100	>100	>100	>100	>100	25	100	50	100	100
XX	100	100	>100	>100	100	>100	12·5	100	100	100	100
XXII	50	>100	100	>100	>100	>100	25	100	100	100	100
XXVI	25	100	100	>100	50	>100	12·5	100	100	100	>100
XXVII	25	100	>100	>100	>100	>100	25	100	50	100	100
XXVIII	100	>100	>100	>100	>100	>100	25	25	25	50	>100
XXIX[e]	>100	>100	100	>100	>100	>100	100	>100	>100	>100	>100

[a] The amines were tested in the form of salts indicated in Table I. [b] 1 *Streptococcus* β-*haemolyticus*, 2 *Streptococcus faecalis*, 3 *Staphylococcus pyogenes aureus*, 4 *Pseudomonas aeruginosa*, 5 *Escherichia coli*, 6 *Proteus vulgaris*, 7 *Mycobacterium tuberculosis* H37Rv, 8 *Saccharomyces pasterianus*, 9 *Trichophyton mentagrophytes*, 10 *Candida albicans*, 11 *Aspergillus niger*. [c] VÚFB-12.247. [d] VÚFB-12.248. [e] VÚFB-12.314, hemihydrate.

Most of the compounds prepared were evaluated by methods of the general pharmacological screening; the amines were tested in the form of salts described in the Experimental. Results are given in Table I. As far as central effects are concerned, it is apparent that in agreement with structure, mild stimulant effects predominate over the depressant ones which appear mostly only in subtoxic doses. The amphetamine character of some of the substances is manifested by their antireserpine and anorectic activity (*XX* and most significant with *XXVI*). Somewhat surprising was the detection of an anticonvulsant effect with the phenethylamine analogue *XIV*. From the other neurotropic activities, it is necessary to mention first a rather significant local anaesthetic effect of *XV*, *XX*, *XXII*, and further a relatively weak spasmolytic effect of the anticholinergic type (*XXII*, *XXVII*); the myotropic spasmolytic activity is more pronounced and attains the intensity of the papaverine activity (*XX*, *XXII*, *XXVII*). With some of the compounds, an adrenolytic effect was found (*XV*, *XVI*, *XVII*, *XXVII*), accompanied partly with brief drops of the blood pressure (*XV–XVII*). From the point of structure–activity relations, it is necessary to point out especially the typical adrenolytic activity of the arylethylpiperazines *XVI* and *XVII*. Compound *XIV* showed a hypoglycaemic effect. The acid *VII* by its structure has some presupposition for antiinflammatory activity; for this reason, it was tested (by Dr J. Grimová, pharmacological department of this institute) in this line but was found practically inactive. The compounds prepared were further evaluated in the *in vitro* tests for antimicrobial activity towards a standard set of microorganisms (Dr J. Turinová and Dr A. Čapek in the bacteriological department of this institute). The results are summarized in Table II in the form of minimum inhibitory concentrations. The inhibitory activity towards mycobacteria and lower fungi is apparent.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected; the samples were dried *in vacuo* (about 0·5 Torr) over P_2O_5 at room temperature or at a higher temperature not exceeding 100°C. The UV spectrum (in methanol) was recorded with a Unicam SP 8000 spectrophotometer, the IR spectra (in Nujol unless stated otherwise) with a Unicam SP 200G spectrophotometer, the ^{1}H-NMR spectra (in $CDCl_3$ unless stated otherwise) on a Tesla BC 487 (80 MHz) spectrometer and the mass spectra with a MS 902 (AEI) spectrometer. The homogeneity of the compounds was checked on thin layers of silica gel. Preparative column chromatography was done on Al_2O_3 (activity II).

(*s*-Hydrindacen-4-yl)acetonitrile (*II*)

A mixture of 26·4 g 98% NaCN and 120 ml dimethyl sulfoxide was heated to 90°C and under stirring treated over 15 min with 82·5 g chloride *I* (ref.[2]). The temperature of the mixture rose spontaneously to 120°C. It was then heated for further 15 min to 100°C and after cooling decomposed by pouring into 1 l water. The separated product was filtered after standing overnight,

washed with water and dried; 77 g (98%), m.p. 77—80°C. This crude product, which does not contain the starting chloride *I*, was used to further work without any purification. It is, however, not homogeneous, and for preparing the analytical sample, chromatography (4·5 g substance was used) on a column of Al_2O_3 (100 g) was necessary. Elution with hexane and then with a mixture of hexane and benzene gave 2·45 g of a homogeneous substance crystallizing from hexane and melting at 97—98°C. IR spectrum (KBr): 860 (solitary Ar—H), 2252 cm^{-1} (R—CN). ^{1}H-NMR spectrum: δ 7·08 (s, 1 H, Ar—H), 3·60 (s, 2 H, $ArCH_2CN$), 2·90 (t, 8 H, 4 $ArCH_2$ of the skeleton), 2·15 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{14}H_{15}N$ (197·3) calculated: 85·23% C, 7·67% H, 7·10% N; found: 85·39% C, 7·84% H, 6·96% N. The more polar fractions from the mentioned chromatography were not obtained in a crystalline state and were not characterized.

(*s*-Hydrindacen-4-yl)acetic Acid (*VII*)

A mixture of 66 g *II*, 60 ml acetic acid, 60 ml water and 60 ml H_2SO_4 was refluxed for 2 h (bath temperature 160—170°C). After pouring into 700 ml water, the mixture was left overnight at room temperature. The crude product was isolated by filtration, dissolved in a solution of 22 g NaOH in 600 ml water, and after filtration, precipitated again with 100 ml 1 : 1 dilute hydrochloric acid; 58 g (80%), m.p. 154—157°C (probably a solvate). The pure compound was obtained by crystallization first from a mixture of benzene and hexane and then from cyclohexane; m.p. 185—186°C. IR spectrum: 860 (solitary Ar—H), 940, 1249, 1292, 1702, 2660 cm^{-1} (COOH). For $C_{14}H_{16}O_2$ (216·3) calculated: 77·75% C, 7·45% H; found: 78·02% C, 7·76% H.

(*s*-Hydrindacen-4-yl)acetyl Chloride (*VIII*)

A solution of 16·6 g *VII* in 100 ml benzene was treated with 17 ml $SOCl_2$ and the mixture refluxed for 1·5 h. Volatile components were then evaporated *in vacuo* (bath temperature 60°C). The residue (18·0 g, theoretical yield) is the crude product crystallizing on standing. It was used to further work without purification.

Ethyl (*s*-Hydrindacen-4-yl)acetate (*IX*)

A solution of 2·0 g crude *VIII* in 20 ml benzene was treated dropwise with a solution of 1·2 ml pyridine in 10 ml ethanol and the mixture was refluxed for 1 h. After evaporation under reduced pressure, the residue was diluted with benzene, the solution was washed with 10% hydrochloric acid, 20% solution of Na_2CO_3 and with water, and after drying (Na_2SO_4), it was processed by distillation; 1·6 g (77%), b.p. 160°C/1 Torr, n_D^{22} 1·5418. ^{1}H-NMR spectrum: δ 6·85 (s, 1 H, Ar—H), 4·05 (q, 2 H, $COOCH_2$), 3·60 (s, 2 H, $ArCH_2CO$), 2·80 (t, 8 H, 4 $ArCH_3$ of the skeleton), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·18 (t, 3 H, C—CH_3). For $C_{16}H_{20}O_2$ (244·3) calculated: 78·65% C, 8·25% H; found: 79·16% C, 8·26% H.

2-(*s*-Hydrindacen-4-yl)ethanol (*XIII*)

A solution of 1·3 g *IX* in 25 ml ether was reduced by refluxing with 0·5 g $LiAlH_4$ for 2·5 h. After cooling, the mixture was decomposed with 2 ml 20% NaOH, after 30 min of stirring, the solid was filtered off, washed with ether and the filtrate was evaporated. There were obtained 1·08 g (theoretical yield) of a product which was recrystallized from hexane, m.p. 115—116°C. IR spectrum: 861 (solitary Ar—H), 1011, 1031, 1044 (CH_2OH), 3330, 3395 cm^{-1} (OH). ^{1}H-NMR spectrum: δ 6·90 (s, 1 H, Ar—H), 3·68 (t, J = 7·0 Hz, 2 H, CH_2O), 2·80 (t and d, 10 H,

5 $ArCH_2$), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·95 (s, 1 H, OH). Mass spectrum with the molecular ion of *m/e* 202 indicates the composition $C_{14}H_{18}O$; the most intensive fragment, *m/e* 171. For $C_{14}H_{18}O$ (202·3) calculated: 83·12% C, 8·97% H; found: 83·04% C, 8·92% H.

4-Methyl-(*s*-hydrindacen-4-yl)acetopiperazide (*X*)

A solution of 12·0 g crude *VIII* in 60 ml benzene was stirred and treated dropwise over 5 min with a solution of 10·5 g 1-methylpiperazine in 80 ml benzene. The mixture was stirred for 1·5 h without heating (a spontaneous rise of temperature took place) and then shaken with a mixture of 30 ml hydrochloric acid and 400 ml water. The separated hydrochloride of the product was filtered, suspended in the aqueous layer of the filtrate and the suspension was made alkaline with 20% NaOH. The separated crystalline base was filtered, washed with water and dried *in vacuo*; 10·0 g (66%), m.p. 144—147°C. The analytical sample was obtained by crystallization from cyclohexane; m.p. 154—155°C. IR spectrum (KBr): 859 (solitary Ar—H), 1 640 (CO—N), 2795 cm^{-1} (N—CH_3). ^{1}H-NMR spectrum: δ 6·98 (s, 1 H, Ar—H), 3·59 (s, 2 H, $ArCH_2CO$), *c.* 3·50 (m, 4 H, $CH_2N^1CH_2$ of piperazine), 2·82 (t, 4 H, 2 $ArCH_2$ in positions 3 and 5), 2·72 (t, 4 H, 2 $ArCH_2$ in positions 1 and 7), *c.* 2·25 (m, 4 H, $CH_2N^4CH_2$ of piperazine), 2·20 (s, 3 H, NCH_3), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{19}H_{26}N_2O$ (298·4) calculated: 76·46% C, 8·78% H, 9·39% N; found: 76·68% C, 8·81% H, 9·41% N.

4-(2-Hydroxyethyl)-(*s*-hydrindacen-4-yl)acetopiperazide (*XI*)

A solution of 18 g *VIII* in 200 ml benzene was stirred and treated dropwise with a solution of 11 g 1-(2-hydroxyethyl)piperazine and 8·0 g triethylamine in 60 ml benzene and the mixture was heated for 1 h to 55—60°C. It was then processed similarly as in the foregoing case. There were obtained 14·6 g (58%) of the desired base and a sample was recrystallized from a mixture of cyclohexane and benzene; m.p. 141—142°C. IR spectrum: 861 (solitary Ar—H), 996, 1 047 (CH_2OH), 1 640 (CO—N), 3 190 cm^{-1} (OH). For $C_{20}H_{28}N_2O_2$ (328·4) calculated: 73·14% C, 8·59% H, 8·53% N; found: 72·97% C, 8·73% H, 8·86% N.

2-(*s*-Hydrindacen-4-yl)ethylamine (*XIV*)

A solution of 20 g *II* in a mixture of 100 ml ether and 50 ml benzene was added dropwise to a stirred suspension of 7·0 g $LiAlH_4$ in 100 ml ether and the mixture was refluxed for 5 h. After cooling, it was decomposed under stirring with 28 ml 20% NaOH added dropwise, after 30 min of stirring, the solid was filtered off and washed with ether. The filtrate was evaporated and gave 20·8 g (100%) crude base boiling at 131°C/1 Torr. The hydrochloride was obtained by neutralization of the base in ethereal solution with an ethanolic solution of hydrogen chloride; m.p. 276 to 277°C (aqueous ethanol). For $C_{14}H_{20}ClN$ (237·8) calculated: 70·72% C, 8·48% H, 14·91% Cl, 5·89% N; found: 71·05% C, 8·58% H, 15·02% Cl, 5·56% N.

1-[2-(*s*-Hydrindacen-4-yl)ethyl]-4-methylpiperazine (*XVI*)

A solution of 9·2 g *X* in 70 ml warm benzene was added dropwise to a suspension of 4·0 g $LiAlH_4$ in 60 ml ether and the mixture was refluxed for 2·5 h. Processing like in the foregoing case yielded 8·7 g (99%) of an oily base which was converted to the dihydrochloride, m.p. over 280°C (aqueous 2-propanol). The analysis indicates the substance to be a hemihydrate. For $C_{19}H_{30}Cl_2N_2O$ + + 0·5 H_2O (366·4) calculated: 62·25% C, 8·54% H, 19·36% Cl, 7·65% N; found: 61·75% C, 8·59% H, 18·73% Cl, 7·64% N.

1-[2-(*s*-Hydrindacen-4-yl)ethyl]-4-(2-hydroxyethyl)piperazine (*XVII*)

Like in the preceding case, 10·0 g *XI* was reduced with 4·0 g $LiAlH_4$ in a mixture of 70 ml ether and 120 ml benzene. There were obtained 9·7 g (100%) crude oily base. The dihydrochloride crystallized from aqueous ethanol as a hemihydrate, m.p. 239—240°C. For $C_{20}H_{22}Cl_2N_2O$ + + 0·5 H_2O (396·4) calculated: 60·59% C, 8·40% H, 17·89% Cl, 7·07% N; found: 60·12% C, 8·31% H, 17·80% Cl, 6·70% N.

(*s*-Hydrindacen-4-yl)acetone (*XII*)

A mixture of 10·7 g Mg, 10 ml ethanol and 1 ml CCl_4 was heated for starting the reaction; 130 ml ether were then slowly added dropwise. The refluxing mixture was treated dropwise over 45 min with a solution of 70·4 g diethyl malonate in a mixture of 40 ml ethanol and 50 ml ether and refluxing was continued until complete dissolution of Mg was attained (approximately 12 h). The mixture was then stirred and treated dropwise over 30 min with a solution of 93·8 g crude *VIII* in 400 ml ether and refluxing was continued for another 30 min. After cooling and under external cooling with water, it was decomposed with a cold solution of 35 ml H_2SO_4 in 320 ml water, the organic layer was separated, washed with water and evaporated. The residue (152 g) was treated with 120 ml acetic acid, 80 ml water and 16 ml H_2SO_4 and the mixture was refluxed for 5 h. After cooling, it was made alkaline with 600 ml 20% NaOH and the product was isolated by extraction with a mixture of benzene and ether. The extract was washed with water, dried with Na_2SO_4 and evaporated. Distillation of the residue gave 43·8 g (52%) product boiling at 152—154°C/2·2 Torr. On standing, the product crystallized and after crystallization from hexane melted at 77—78°C. IR spectrum: 861 (solitary Ar—H), 1589 (Ar), 1720 cm^{-1} (RCOR'). ^{1}H-NMR spectrum: δ 7·00 (s, 1 H, Ar—H), 3·60 (s, 2 H, $ArCH_2CO$), 2·82 (t, 4 H, 2 $ArCH_2$ in positions 3 and 5), 2·72 (t, 4 H, 2 $ArCH_2$ in positions 1 and 7), 2·10 (s, 3H, CH_3), *c.* 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6). For $C_{15}H_{18}O$ (214·3) calculated: 84·06% C, 8·47% H; found: 83·99% C, 8·60% H.

The mentioned distillation gave in addition to ketone *XII* 17 g of a solid distillation residue consisting, according to thin-layer chromatography, of two other substances, both of them being more polar than the ketone *XII*. The mixture was chromatographed on a column of 360 g Al_2O_3 using benzene as eluent. There were eluted first 0·48 g of the least polar, oily component which was not investigated. In further fractions, 9·62 g of a homogeneous substance were eluted, melting after crystallization from ethanol at 117—118°C, which was identified as (8-methylthio--*s*-hydrindacen-4-yl)acetone (*XVIII*). UV spectrum: λ_{max} 223 nm infl. (log ε 4·25), 270 nm (3·82), infl. 283 nm (3·68), 293 nm (3·62). IR spectrum: 969, 1166, 1330, 1360, 1379, 1717 cm^{-1} (RCOR'). ^{1}H-NMR spectrum: δ 3·60 (s, 2 H, $ArCH_2CO$), 2·98 and 2·85 (2 t, 8 H, 4 $ArCH_2$ of the skeleton), 2·20 and 2·08 (2 s, 6 H, SCH_3 and $COCH_3$), *c.* 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6). The mass spectrum with a molecular ion at *m/e* 260 suggests the formula $C_{16}H_{20}OS$; the most intensive fragment, *m/e* 245. For $C_{16}H_{20}OS$ (260·3) calculated: 73·82% C, 7·74% H, 12·30% S; found: 73·83% C, 7·78% H, 11·95% S.

Continuation of the chromatography with the elution with benzene led to the isolation of 1·8 g of a homogeneous substance, crystallizing from ethanol and melting at 192—193°C. It was identified as bis[8-(2-oxopropyl)-*s*-hydrindacen-4-yl]methane (*XIX*). ^{1}H-NMR spectrum: δ 3·82 (s, 2 H, CH_2 of the methane residue), 3·55 (s, 4 H, 2 $ArCH_2CO$), 2·68 and 2·54 (2 t, 16 H, 8 $ArCH_2$ of two hydrindacene moieties), 2·02 (s, 6 H, 2 $COCH_3$), 2·00 (m, 8 H, 4 CH_2 in positions 2, 6, 2' and 6'). The mass spectrum, showing the molecular ion at *m/e* 440, suggests the formula $C_{31}H_{36}$· .O_2; basic fragment, *m/e* 226. For $C_{31}H_{36}O_2$ (440·6) calculated: 84·50% C, 8·24% H; found: 84·50% C, 8·33% H.

(*s*-Hydrindacen-4-yl)acetone Oxime (*VI*)

A mixture of 20·0 g *XII*, 150 ml ethanol, 33·5 g $NH_2OH.HCl$ and 45 ml pyridine was refluxed for 15 h. Volatile components were evaporated under reduced pressure, the residue treated with 400 ml water, the separated product filtered, washed with water and dried; 19·4 g (91%), m.p. 145–152°C. Analytical sample was obtained by crystallization from aqueous ethanol, m.p. 163–164°C. IR spectrum: 859 (solitary Ar—H), 1 632 (C=N), 3 245 cm^{-1} (OH). ^{1}H-NMR spectrum (CD_3SOCD_3): δ 10·25 (bs, 1 H, NOH), 6·80 (s, 1 H, Ar—H), 3·26 (s, 2 H, $ArCH_2$ of the side chain), 2·68 (t, 8 H, 4 $ArCH_2$ of the skeleton), *c.* 1·90 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·53 (s, 3 H, CH_3). For $C_{15}H_{19}NO$ (229·3) calculated: 78·56% C, 8·35% H, 6·11% N; found: 78·66% C, 8·62% H, 6·29% N.

1-(*s*-Hydrindacen-4-yl)-2-methyl-2-propanol (*XXIV*)

Grignard reagent was prepared from 4·5 g Mg and 28·4 g methyl iodide in 100 ml ether. At room temperature, it was treated under stirring over 45 min with a solution of 34·3 g *XII* in a mixture of 50 ml benzene and 150 ml ether. The mixture was refluxed for 4 h and after cooling decomposed with a solution of 20 g NH_4Cl in 100 ml water. After separation, the aqueous layer was extracted with a mixture 2 : 1 of ether and benzene, organic solutions were combined, washed with 10% solution of $Na_2S_2O_3$, and after drying (Na_2SO_4) evaporated *in vacuo* (bath temperature 45°C). The remaining oil (36·8 g, 100%) crystallized on standing; m.p. 82–83°C (hexane). IR spectrum: 865, 895 (solitary Ar—H), 1150 (R_3C—OH), 1580, 1609 (Ar), 3310 cm^{-1} (OH). For $C_{16}H_{22}O$ (230·3) calculated: 83·42% C, 9·63% H; found: 83·21% C, 9·86% H.

N-[1-(*s*-Hydrindacen-4-yl)-2-methyl-2-propyl]formamide (*XXV*)

A solution of 36 g *XXIV* in 50 ml acetic acid was cooled (temperature below 10°C) and treated with a mixture of 10 ml acetic acid and 10 ml H_2SO_4 and then slowly with 20 g NaCN under stirring. After 15 min of stirring, a mixture of 20 ml acetic acid and 30 ml H_2SO_4 was added under steady cooling, the mixture was stirred for 4 h and then left for 48 h at room temperature. It was then decomposed by pouring into a mixture of 400 g ice and 250 ml water; under cooling, it was neutralized by a slow addition of 450 ml 20% NaOH (to a pH of 8). The separated product was isolated by extraction with benzene, the extract was dried and evaporated; 36 g of a solid, brown residue. Crystallization from hexane gave 24 g (60%) of a substance melting at 112–115°C. Analytical sample was obtained by crystallization from cyclohexane; m.p. 130–131°C. IR spectrum (KBr): 870 (solitary Ar—H), 1380 (CH_3—C—CH_3), 1690 (HCO—NH), 3210 cm^{-1} (NH). ^{1}H-NMR spectrum: δ 7·85 and 7·92 (2 d, J = 10·0 Hz, 1 H, CHO), 6·95 (s, 1 H, Ar—H), 6·30 and 5·55 (d, J = 10·0 Hz, and bs, 1 H, NH), 2·80 (t, 8 H, 4 $ArCH_2$ of the skeleton), 2·70 and 3·00 (2 s, 2 H, $ArCH_2$ of the side chain), *c.* 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·35 and 1·38 (2 s, 6 H, 2 CH_3); the doubling of some signals indicates the presence of an impurity, probably of an isomer. For $C_{17}H_{23}NO$ (257·4) calculated: 79·33% C, 9·01% H, 5·44% N; found: 79·53% C, 9·02% H, 5·32% N.

1-(*s*-Hydrindacen-4-yl)-2-propylamine (*XX*)

A solution of 19 g *VI* in 300 ml ethanol was added dropwise to 42 g Na, 120 ml ethanol were then slowly added and the mixture refluxed until the complete dissolution of Na. It was decomposed with 150 ml water, ethanol was evaporated under reduced pressure and the oily base was isolated from the residue by extraction with benzene; 15·9 g (90%). The hydrochloride

crystallized from ethanol and melted at 249—250°C. For $C_{15}H_{22}ClN$ (251·8) calculated: 71·55% C, 8·81% H, 14·08% Cl, 5·56% N; found: 71·45% C, 8·92% H, 14·13% Cl, 5·17% N.

1-(*s*-Hydrindacen-4-yl)-2-methyl-2-propylamine (*XXVI*)

A solution of *XXV* (7·5 g) in warm ethanol (35 ml) was treated with a solution of 3·5 g NaOH in 20 ml water and the mixture was refluxed for 48 h. Ethanol was evaporated under reduced pressure, the residue diluted with water and the basic product isolated by extraction with a mixture of benzene and ether. The extract was shaken with a mixture of 10 ml hydrochloric acid and 40 ml water, the separated hydrochloride of the product was filtered, washed with water and ether, and dried; 7·80 g (100%), m.p. over 310°C (aqueous ethanol). For $C_{16}H_{24}ClN$ (265·8) calculated: 72·30% C, 9·10% H, 13·33% Cl, 5·27% N; found: 72·19% C, 9·28% H, 13·39% Cl, 5·20% N.

Decomposition of the hydrochloride with 20% NaOH released the base which was isolated by extraction with a mixture of ether and benzene and purified by distillation; b.p. 158—160°/1·5 Torr, n_D^{22} 1·5582. ^{1}H-NMR spectrum: δ 6·95 (s, 1 H, Ar—H), 2·80 (t, 8 H, 4 $ArCH_2$ of the skeleton), 2·68 (s, 2 H, $ArCH_2$ of the side chain), *c.* 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·45 (s, disappears after D_2O, 2 H, NH_2), 1·12 (s, 6 H, CH_3—C—CH_3). For $C_{16}H_{23}N$ (229·4) calculated: 83·78% C, 10·11% H, 6·11% N; found: 83·81% C, 9·97% H, 5·75% N.

N-[1-(*s*-Hydrindacen-4-yl)-2-propyl]formamide (*XXI*)

A mixture of 4·8 g *XX* and 10 ml ethyl formate was heated in an autoclave for 6 h to 120—130°C. After cooling, it was diluted with ethanol and the solution evaporated under reduced pressure. The residue was dissolved in 140 ml benzene, the solution washed with dilute hydrochloric acid and a 5% solution of Na_2CO_3, dried and evaporated; 5·45 g (100%) of a solid. Analytical sample was obtained by crystallization from a mixture of benzene and hexane; m.p. 127—128°C. IR spectrum: 861 (solitary Ar—H), 1540 (Ar). 1652, 1679 (HCO—NH), 3280 cm^{-1} (NH). For $C_{16}H_{21}NO$ (243·3) calculated: 78·96% C, 8·70% H, 5·76% N; found: 79·30% C, 8·84% H, 5·47% N.

N-Methyl-1-(*s*-hydrindacen-4-yl)-2-propylamine (*XXII*)

A solution of 5·0 g *XXI* in 50 ml benzene was added dropwise to a suspension of 2·0 g $LiAlH_4$ in 50 ml ether and the mixture was refluxed for 2 h. After cooling, it was decomposed by addition of 8 ml 20% NaOH, after 30 min of stirring, the solid was filtered off and washed with ether. The filtrate was shaken with a mixture of 6 ml hydrochloric acid and 40 ml water, the aqueous layer together with the oily hydrochloride was separated, made alkaline with 20% NaOH and the released base isolated by extraction with a mixture of benzene and ether. The extract was dried with Na_2SO_4 and after filtration neutralized with an ethanolic solution of hydrogen chloride. Evaporation of the mixture gave a solid hydrochloride, which was mixed with ether and filtered; 5·30 g (97%), m.p. 175—177°C. The analytical sample melted at 180—181°C (ethanol–ether). For $C_{16}H_{24}ClN$ (265·8) calculated: 72·29% C, 9·10% H, 13·34% Cl, 5·27% N; found: 72·26% C, 9·02% H, 13·49% Cl, 5·35% N.

N-Methyl-1-(*s*-hydrindacen-4-yl)-2-methyl-2-propylamine (*XXVII*)

Like in the preceding case, 15·0 g *XXV* were reduced with 4·0 g $LiAlH_4$ in a mixture of 50 ml ether and 100 ml benzene. A similar processing yielded 15·0 g (92%) hydrochloride, m.p. 292 to

293°C (ethanol). For $C_{17}H_{26}ClN$ (279·8) calculated: 72·95% C, 9·37% H, 12·67% Cl, 5·01% N; found: 72·67% C, 9·56% H, 12·63% Cl, 4·93% N.

Decomposition of the hydrochloride with 20% NaOH and extraction with benzene gave the base, b.p. 165—168°C/1·5 Torr; the distillate solidified to a substance melting at 57°C. ^{1}H-NMR spectrum: δ 6·98 (s, 1 H, Ar—H), 2·86 (t, 8 H, 4 $ArCH_2$ of the skeleton), 2·72 (s, 2 H, $ArCH_2$ of the side chain), 2·35 (s, 3 H, N—CH_3), 2·00 (m, 4 H, 2 CH_2 in positions 2 and 6), 1·28 (bs, 1 H, NH), 1·10 (s, 6 H, CH_3—C—CH_3). For $C_{17}H_{25}N$ (243·4) calculated: 83·88% C, 10·36% H, 5·76% N; found: 84·19% C, 10·13% H, 5·82% N.

N,N-Dimethyl-2-(*s*-hydrindacen-4-yl)ethylamine (*XV*)

A solution of 10·0 g *XIV* in a mixture of 10 ml 85% formic acid and 13 ml water was treated with 15 ml 37% aqueous formaldehyde and the mixture was refluxed for 5 h (bath temperature 110—120°C). After cooling, 30 ml hydrochloric acid were added, and the mixture was evaporated *in vacuo*. The residue was dissolved in 70 ml water, the solution filtered and the filtrate made alkaline with 20% NaOH. The base was isolated by extraction with a mixture of benzene and ether, the extract was dried with solid KOH and processed by distillation; 8·0 g (70%), b.p. 144—145°C/1 Torr, n_D^{22} 1·5443. For $C_{16}H_{23}N$ (229·3) calculated: 83·78% C, 10·11% H, 6·11% N; found: 84·04% C, 9·80% H, 6·03% N.

The hydrochloride was obtained by neutralization of the base in ether with an ethanolic solution of hydrogen chloride; m.p. 255—256°C (ethanol). For $C_{16}H_{24}ClN$ (265·8) calculated: 72·30% C, 9·10% H, 13·33% Cl, 5·27% N; found: 72·33% C, 9·21% H, 13·18% Cl, 4·95% N.

N,N-Dimethyl-1-(*s*-hydrindacen-4-yl)-2-propylamine (*XXIII*)

Like in the preceding case, 4·8 g *XX* were methylated with 6 ml 85% formic acid and 10 ml 37% aqueous formaldehyde in the presence of 10 ml water. There were obtained 5·50 g (100%) of a crude, oily base, a sample of which distills at 156°C/1 Torr. Like in the preceding case, the hydrochloride was prepared, crystallizing from a mixture of 95% ethanol and ether as a hemihydrate, m.p. 181—182°C. For $C_{17}H_{26}ClN + 0{\cdot}5\ H_2O$ (288·9) calculated: 70·68% C, 9·42% H, 4·85% N; found: 70·55% C, 9·15% H, 4·57% N.

N,N-Dimethyl-1-(*s*-hydrindacen-4-yl)-2-methyl-2-propylamine (*XXVIII*)

Like in the preceding cases, a mixture of 5·2 g *XXVI* and 5·6 g *XXVII* was methylated with 12 ml 98% formic acid and 20 ml 38% aqueous formaldehyde in the presence of 20 ml water. There were obtained 10·0 g (75%) hydrochloride, m.p. 265—266°C (ethanol–ether). For $C_{18}H_{28}ClN$ (293·9) calculated: 73·56% C, 9·60% H, 12·07% Cl, 4·77% N; found: 73·68% C, 9·55% H, 12·21% Cl, 4·68% N.

From the mother liquor after the hydrochloride, the base was released, which is oily and distills at 173—175°C/1 Torr; 2·5 g (the total yield is thus 96%). For $C_{18}H_{27}N$ (257·4) calculated: 5·44% N; found: 5·06% N.

The methiodide (*XXIX*) was prepared by treatment of the base *XXVIII* with an excess of methyl iodide in ether, m.p. 224—225°C. The analysis suggests it to be a hemihydrate. For $C_{19}H_{30}$·.IN + 0·5 H_2O (408·4) calculated: 55·92% C, 7·62% H, 31·08% I, 3·43% N; found: 56·34% C, 7·25% H, 30·89% I, 3·61% N.

Diethyl Formamido(*s*-hydrindacen-4-ylmethyl)malonate (*III*)

Diethyl formamidomalonate[11,12] (5·08 g) was added to a solution of sodium ethoxide (0·57 g Na, 55 ml ethanol) and the mixture was stirred for 30 min at room temperature and for 10 min at 50°C. The chloride *I* (5·15 g) and a few crystals of KI were then added and the mixture was stirred for 7 h at room temperature, for 5 h at 70—80°C and finally for 2 h at room temperature. It was decomposed by pouring into 220 ml water. After standing overnight, the separated substance was filtered, washed with water and dried; 7·1 g (76%). Analytical sample was obtained by crystallization from ethanol, m.p. 133—134°C. IR spectrum: 859 (solitary Ar—H), 1189, 1221, 1236 (C—O—C), 1491 (Ar), 1657, 1678 (HCO—NH), 1745 (COOR), 3315 cm^{-1} (NH). For C_{21}. $.H_{27}NO_5$ (373·4) calculated: 67·53% C, 7·29% H, 3·75% N; found: 67·60% C, 7·25% H, 3·83% N.

Formamido(*s*-hydrindacen-4-ylmethyl)malonic Acid (*IV*)

A mixture of 3·1 g *III*, 20 ml ethanol, 16 ml water and 2·26 g NaOH was refluxed for 4 h. Ethanol was evaporated under reduced pressure (bath temperature 60°C), the residue was dissolved in 80 ml warm water and the solution was filtered with charcoal after 24 h of standing. The filtrate was cooled and acidified with 30 ml hydrochloric acid. After standing overnight, the separated acid was filtered, washed with water and dried; 1·42 g (55%), m.p. 215—216°C (capillary). IR spectrum (KBr): 867 (solitary Ar—H), 909, 1220, 1740, 1757, 2620 (COOH), 1510, 1630 (HCO—NH), 3280 cm^{-1} (NH). For $C_{17}H_{19}NO_5$ (317·3) calculated: 64·33% C, 6·04% H, 4·41% N; found: 64·44% C, 6·33% H, 4·47% N.

2-Amino-3-(*s*-hydrindacen-4-yl)propionic Acid (*V*)

A mixture of 0·9 g *IV* and 15 ml 1M-HCl was refluxed for 8 h giving a clear solution. It was evaporated *in vacuo* and the residue dissolved in a warm mixture of 20 ml water and 10 ml ethanol. The solution was filtered with charcoal and the filtrate evaporated again. There were obtained 0·8 g hydrochloride which crystallized from a mixture of ethanol and ether as a solvate with 1 molecule of ethanol, m.p. 225—226°C. For $C_{15}H_{20}ClNO_2 + C_2H_6O$ (327·8) calculated: 62·27% C, 8·00% H, 10·82% Cl, 4·27% N; found: 62·24% C, 7·39% H, 10·63% Cl, 4·59% N.

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